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The First Successful Base-Promoted Isomerization of Propargyl Amides to Chiral Ynamides. Applications in Ring-Closing Metathesis of Ene–Ynamides and Tandem RCM of Diene–Ynamides

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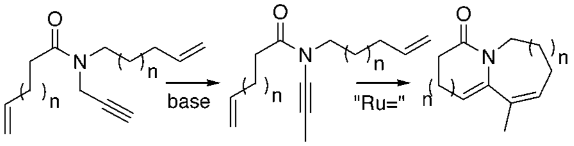
ABSTRACT



A highly useful sequence of reactions is described here. These reactions consist of the first successful base-induced isomerizations of propargyl amides to chiral ynamides, applications of these novel ynamides in ring-closure metathesis leading to chiral 2-amidodienes useful for Diels–Alder cycloadditions, and the first successful tandem RCM of diene–ynamides.

Synthetic utility of ynamides and allenamides, electron-deficient variants of ynamines and allenamines, respectively, has recently attracted much attention in the literature.[1−6] Ynamides and allenamides offer superior thermal stability[7,8] and comparable reactivity relative to ynamines and allenamines. The combination of this improved stability and sufficient reactivity has rendered these two classes of functionally rich organic building blocks highly useful for the development of new stereoselective methodologies.[3−6] We have been exploring reactivities of novel ynamides[5] [**2**] and allenamides[6] [**3**] specifically featuring a chiral imida-

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zolidinone or oxazolidinone group [Figure 1]. Our original plan for accessing ynamides **2** via a facile base-induced isomerization of propargyl amides **1** was surprisingly derailed and inadvertently led us to allenamides **3**,[9] although this is a known protocol for synthesis of ynamine.[1,7b] While this failure allowed us to study sparsely investigated allenamides **3**,[6] it also compelled us to access ynamides **2** via an alternative, but less efficient, route involving dehydrohalogenations of Z-β-bromoenamides.[9]

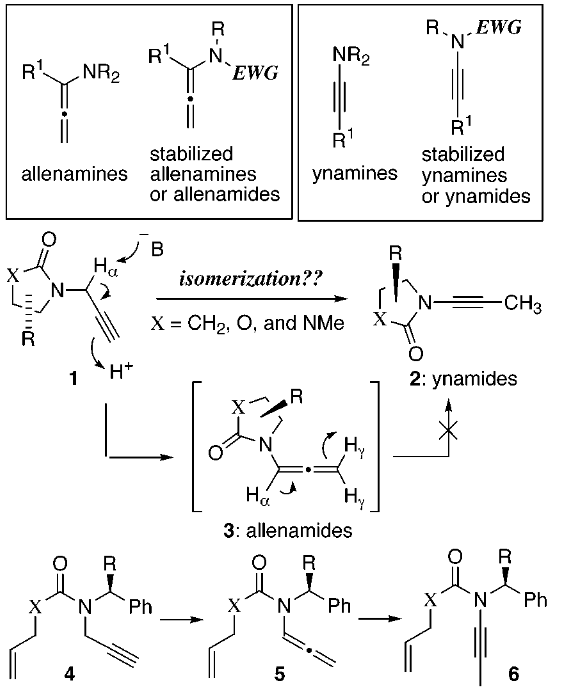
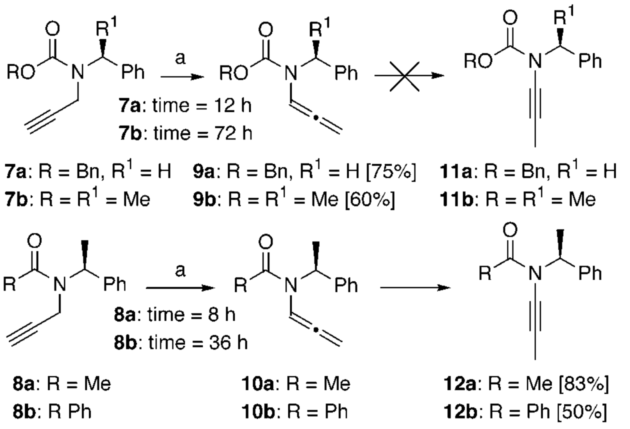


Figure 1.

Although other useful methods such as the use of alkynyl iodonium triflate salts are known for synthesis of 1-sulfonyl amido alkynes,[1,3] a base-induced isomerization protocol remains the most direct and convenient synthetic entry to ynamides. The fundamental questions surrounding this initially failed isomerization, and the need for a practical entry to ynamides provoked us to investigate other propargyl amides **4**. We subsequently found success in the synthesis of ynamides **6**. Ring-closing metathesis [RCM] is a powerful tool in organic synthesis,[10−16] and the new ynamides **6** represent intriguing substrates for enyne metathesis[11,12] leading to useful nitrogen heterocycles.[14] The enyne RCM of C1-heteroatom substituted acetylenes were not known until the elegant studies reported very recently by Kozmin,[13] van Boom,[14] and Mori.[15] We report here our first success in the preparation of ynamides using based-promoted isomerizations as well as applications of these novel ynamides in the first tandem diene−ynamide RCM. To examine based-promoted isomerizations, propargyl urethanes **7a**,**b** and propargyl amides **8a**,**b** were prepared from 1-amino-2-propyne via standard conditions consisting of N-alkylations and N-acylations [Scheme 1].[17] The ensuing isomerizations of **7a**,**b** and **8a**,**b** were carried out using 20 mol % of KOt-Bu/t-BuOH in THF at rt. Propargyl urethanes **7a**,**b** behaved exactly the same as propargyl amides **1** [substituted with an

Scheme 1[a]



[a] (a) THF [0.1 M in concentration], 20 mol % of KOt-Bu, rt.

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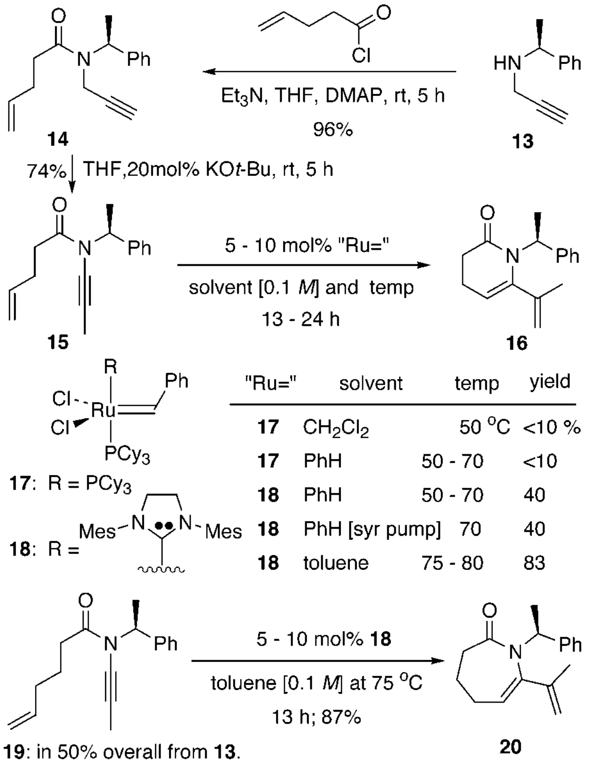
imidazolidinone or oxazolidinone group] with the isomerization being arrested exclusively at allenamide intermediates **9a**,**b**. Conversely, propargyl amides **8a**,**b** completely isomerized to the ynamides **12a**,**b** in 83% and 50% yields, respectively. The length of the reaction time was not a factor in the observed reactivity difference, but the substitution pattern on the nitrogen atom appears to be critical since only the propargyl amide system **8** was successful in the isomerization while propargyl urethanes were not.

Successful isomerization of propargyl amides to ynamides allowed us to explore the synthetic potential of these novel ynamides in RCM. The ynamide **15** was readily prepared in 70% overall yield from the propargyl amine **13** via a sequence consisting of *N*-acylation and KO*t*-Bu/*t*-BuOH-induced isomerization [Scheme 2]. To examine the ene−ynamide ring-closing metathesis closely, the ynamide **15** was subjected to various RCM conditions using Grubbs' Ru catalyst **17** [Scheme 2].[10,11,18−21]

Scheme 2



"Ru="	solvent	temp	yield
17	CH_2Cl_2	50 °C	<10 %
17	PhH	50 - 70	<10
18	PhH	50 - 70	40
18	PhH [syr pump]	70	40
18	toluene	75 - 80	83

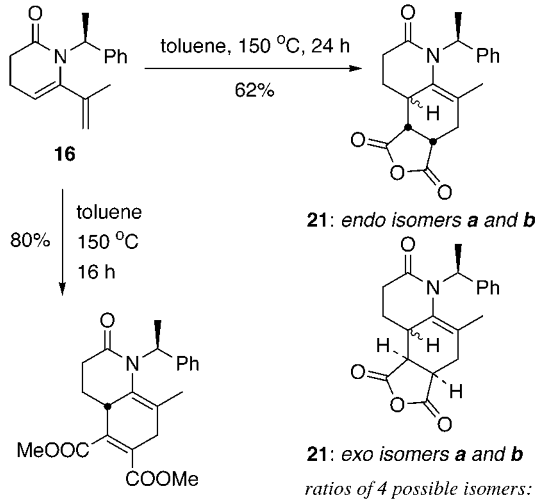
19: in 50% overall from **13**.

It was quickly found that the highly reactive second-generation catalyst **18** developed by Herrmann,[19] Nolan,[20] and Grubbs[21] containing the nucleophilic *N*,*N*-dimestylimidazol-2-ylidene ligand was the most effective in the ene−ynamide RCM. In addition, while syringe pump protocol[16] appeared not to be necessary under these conditions, temperature was critical in the efficiency of this reaction. Under the reaction conditions outlined in Scheme 2, the desired RCM products **16** and **20** were obtained from **15** and **19** [prepared in an analogous manner as **15** from **13** in 50% overall yield] in 83% and 87% yields, respectively.

An immediate proof-of-concept application for these novel chiral 2-amidodienes would be their utility in Diels−Alder cycloaddition reactions. While 1-amino-substituted dienes in Diels−Alder cycloadditions have been well established since pioneering work by Overman and Oppolzer,[22,23] 2-amidodienes have remained relatively less known.[24,25] The ene−ynamide ring-closing metathesis of chiral ynamides offers an excellent entry to highly substituted chiral 2-amido-1,3-dienes.

As shown in Scheme 3, reactions of **16** with dienophiles such as maleic anhydride and dimethyl acetylenedicarboxylate led to the desired cycloadducts **21** and **22** in 62% and 80% yields, respectively. Since diastereoselectivities observed here were only modest, stereochemical assignments were not vigorously pursued. Cycloadducts such as **21** and **22** can be useful, and the resulting chiral enamide functionality could be further manipulated.[26]

Scheme 3



21: *endo isomers* ***a*** *and* ***b***

21: *exo isomers* ***a*** *and* ***b***

22: *dr:* 2 : 1

ratios of 4 possible isomers:
4.5 : 5.0 : 1 : 1

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[17] All new compounds are characterized by ^{1}H NMR, ^{13}C NMR, FTIR, and mass spectroscopy. See Supporting Information for preparations of relevant propargyl amides.

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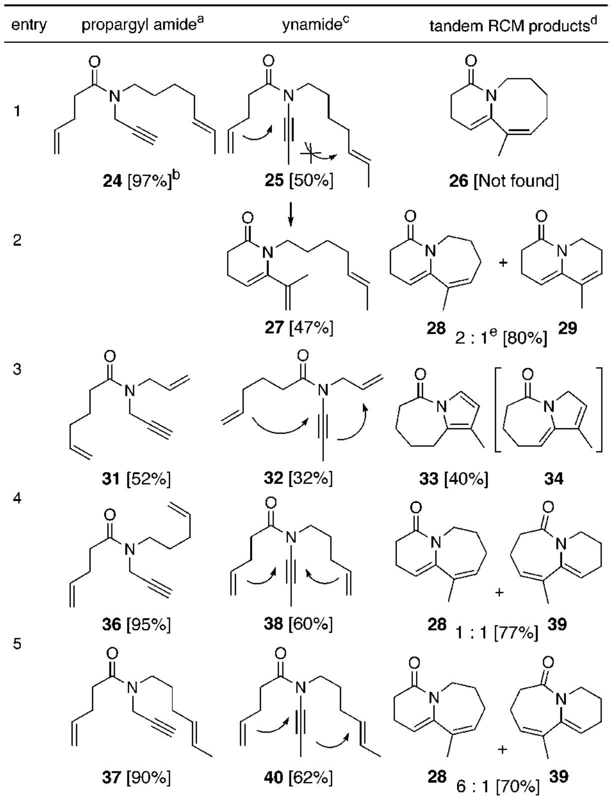
A distinct advantage of ynamides over other heteroatom substituted alkynes is that the nitrogen atom can be tethered with two alkenyl substituents, allowing a tandem RCM. These results are summarized in Table 1. With two sterically differentiated alkenes as shown in **25** [entry 1], the direction of the tandem RCM may be controlled to proceed in the direction shown by the arrows, assuming the metathesis is initiated in an ene−yn−ene manner.[10a,11,13a,15,16] However, the diene ynamide **25** did not lead to the desired 6,8-fused product **26** [entry 1]. Instead, **27** was isolated in 47% yield [entry 2] along with 20−30% of ring-closed products **28** and **29**, suggesting that the second ring-closing was slower given the potential ring size. Interestingly, subjecting **27** to the same conditions provided a mixture of **28** and **29** in 80% overall yield with a ratio of 2:1 [entry 2]. The use of syringe pump addition led to **27** in much lower yield and gave 70% yield of **28** and **29** from **27** with a ratio of 1:1.

Table 1



[a] For entry 1: propargyl amide **24** was prepared from propargyl amine **23** [$HCCCH_2NH(CH_2)_4$-*trans*-$CH{=}CHCH_3$] using $CH_2{=}CH(CH_2)_2COCl$, Et_3N, and DMAP in THF at rt for 8 h. For entry 3: propargyl amide **31** was prepared from propargyl amine **30** [$HCCCH_2NHCH_2CH{=}CH_2$] and $CH_2{=}CH(CH_2)_3COCl$. For entry 4: propargyl amide **36** was prepared from propargyl amine **35a** [$HCCCH_2NH(CH_2)_3CH{=}CH_2$] and $CH_2{=}CH(CH_2)_2$-COCl. For entry 5: propargyl amide **37** was prepared from propargyl amine **35b** [$HCCCH_2NH(CH_2)_3$-*trans*-$CH{=}CHCH_3$] and $CH_2{=}CH(CH_2)_2COCl$. [b] All yields are isolated yields. [c] Isomerizations were carried out using 20 mol % of KO*t*-Bu in THF at rt for 8 h. [d] RCM reactions were carried out using 5−10 mol % of **18** in toluene [0.1 M] at 75 °C for 12 h. [e] All ratios were determined using ^1H NMR.

Compounds **28** and **29** represent the loss of one and two methylene units, respectively, from the side chain in **27**, suggesting that migration of the olefin had occurred prior to the RCM and again that the tether may be too long. This prompted us to examine systems with shorter tethers. The ynamide **32**, prepared in 60% yield from propargyl amide **31** via a successful base-induced isomerization, gave **33** in 40% yield under the same RCM conditions along with an unidentifiable side product [entry 3]. Isolation of the compound **33** suggests that migration of the olefins in the initial tandem ring-closing product **34** had occurred. This favored migration presumably was driven by aromaticity of the resulting pyrrole in **33**.

Encouraged by this result, a fully successful tandem RCM was carried out using ynamides **38** and **40** [entries 4 and 5]. Under the same RCM conditions, **38** gave the desired RCM products **28** and **39** in 77% overall yield with a 1:1 ratio, suggesting that the Ru catalyst initiated RCM from either direction [entry 4]. Thus, by using the ynamide **40** with two sterically differentiated olefinic tethers as we had originally intended, the direction of the tandem RCM was readily controlled to favor the product **28** with an overall yield of 70% [entry 5].

We have communicated here the first successful base-induced isomerization of propargyl amides to chiral ynamides and the immediate application of these novel ynamides in ring-closing metathesis leading to dienamides useful for Diels−Alder cycloadditions. We have also described here the first tandem RCM of diene−ynamides. The application of this useful sequence of new reactions toward the synthesis of natural products is underway.

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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